ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 November 26; 12(33): 6580-6663

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents Thrice Monthly Volume 12 Number 33 November 26, 2024

World Journal of Clinical Cases

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LETTER TO THE EDITOR

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 33 November 26, 2024

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

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World J Clin Cases 2024 November 26; 12(33): 6608-6612

DOI: 10.12998/wjcc.v12.i33.6608

ISSN 2307-8960 (online)

EDITORIAL

Journey to diagnosis: An unfinished exploration of IgG4-related sclerosing cholangitis

Ming-Xing Liang, Ya Chen, Ya He, Yi-Huai He

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade D
Creativity or Innovation: Grade D
Scientific Significance: Grade B

P-Reviewer: Kazi IA

Received: July 4, 2024
Revised: August 19, 2024
Accepted: August 23, 2024
Published online: November 26, 2024
Processing time: 84 Days and 12.1 Hours

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Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is an inflammatory disease that leads to bile duct stricture, characterized by the infiltration of IgG4-positive plasma cells into the bile duct wall, thickening of the bile duct wall, and narrowing of the lumen. The differential diagnosis of IgG4-SC mainly includes primary sclerosing cholangitis, cholangiocarcinoma, and pancreatic cancer. IgG4-SC is often associated with autoimmune pancreatitis and can be accurately diagnosed based on clinical diagnostic criteria. However, isolated IgG4-SC is difficult to distinguish from biliary tumors. Given the significant differences in biological behavior, treatment, and prognosis between these diseases, accurately identifying isolated IgG4-SC has very important clinical significance.

Key Words: Isolated IgG4-associated sclerosing cholangitis; Cholangiocarcinoma; Autoimmune pancreatitis; IgG4-related diseases; Diagnosis and differential diagnosis

Core Tip: Isolated IgG4-related sclerosing cholangitis (IgG4-SC) shares similar clinical manifestations to bile duct tumors, yet they differ significantly in biological behavior, treatment, and prognosis. Therefore, an accurate diagnosis of isolated IgG4-SC is crucial for the clinical management of patients. This article will delve into the key diagnostic points, difficulties, and challenges of isolated IgG4-SC to aid in better identifying and managing this disease.

Citation: Liang MX, Chen Y, He Y, He YH. Journey to diagnosis: An unfinished exploration of IgG4-related sclerosing cholangitis. *World J Clin Cases* 2024; 12(33): 6608-6612
URL: https://www.wjgnet.com/2307-8960/full/v12/i33/6608.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i33.6608

INTRODUCTION

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis, featuring dense infiltration of IgG4-positive plasma cells and extensive fibrosis in the bile duct walls[1]. It is considered an immune-mediated inflammatory disease characterized by pancreaticobiliary inflammatory lesions, thickening of the bile duct wall, and extensive lymphocyte infiltration into the bile duct walls, leading to progressive narrowing and destruction of the bile ducts, along with elevated serum IgG4 levels[2].

This condition is a benign disease, and only a minority of patients who develop IgG4-SC will progress to liver cirrhosis or cholangiocarcinoma[3]. Currently, glucocorticoids are recommended as the first-line treatment for IgG4-SC[4], with a generally favorable prognosis for most patients. Early diagnosis and treatment of IgG4-SC remain crucial to prevent disease progression. Studies have shown that persistent inflammation leads to genomic instability and increases the risk of genetic mutations[5]. For instance, chronic inflammation drives the development of essential thrombocythemia through the activation of Janus kinase 2[6,7], further complicating the diagnosis of IgG4-SC. IgG4-SC is often associated with autoimmune pancreatitis (AIP) and is considered a biliary manifestation of IgG4-related disease (IgG4-RD)[2]. The clinical features of IgG4-SC include cholestatic manifestations such as jaundice and pruritus, however, these clinical presentations have poor specificity for diagnosing IgG4-SC. Therefore, the diagnosis of IgG4-SC is challenging, with a high risk of underdiagnosis or misdiagnosis. However, as time progresses and medical research delves deeper, corresponding diagnostic criteria have gradually been established. Nevertheless, diagnosing IgG4-SC still poses challenges at present.

The HISORt criteria, encompassing histology, imaging, serology, other organ involvement, and response to therapy, are frequently used in the United States and Europe to diagnose IgG4-SC or IgG4-associated cholangitis[8,9]. In 2012, the Japan Biliary Association established clinical diagnostic criteria for IgG4-SC[10]. In 2019, clinical practice guidelines for IgG4-SC were published[11]. Additionally, in 2022, a Japanese group proposed new clinical diagnostic criteria based on revisions to the 2012 clinical diagnostic standards[4], to address the shortcomings of the 2012 diagnostic criteria and provide more detailed diagnoses. When IgG4-SC is associated with AIP or other IgG4-RD, the diagnosis is relatively straightforward. However, diagnosing special types of IgG4-SC, such as isolated IgG4-SC, remains challenging[12,13]. These patients are sometimes misdiagnosed with cholangiocarcinoma and undergo unnecessary surgical resection.

THE DIAGNOSTIC CHALLENGES OF ISOLATED IGG4-SC

Serum IgG4 Levels are one of the most important markers for diagnosing IgG4-RD. However, in isolated IgG4-SC, serum IgG4 may be negative or slightly elevated, primarily presenting as obstructive jaundice with IgG4-positive plasma cell infiltration and frequent bile duct wall thickening[12,14]. These patients are sometimes misdiagnosed with cholangiocarcinoma and undergo surgical resection. Many researchers recommend endoscopic biopsy and immunostaining of tissue samples to determine the presence of IgG4, as this can provide strong diagnostic evidence[15], and is important for ruling out cholangiocarcinoma. However, obtaining sufficiently large characteristic pathological samples of IgG4-SC through endoscopic biopsy is challenging[16], as the obtained specimens are usually small and cannot be used to fully observe the entire range of lymphoplasmacytic sclerosing cholangitis. Additionally, studies have found IgG4-positive cells in primary sclerosing cholangitis (PSC) and cholangiocarcinoma. This finding indicates that relying solely on the detection of IgG4-positive cells as a specific diagnostic foundation may not be sufficient, as its specificity is highly controversial[17,18]. Therefore, the diagnosis of isolated IgG4-SC typically relies on imaging studies.

Ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic US (EUS), and intraductal US (IDUS) are used to assess bile duct abnormalities[19,20]. IgG4-SC associated inflammation most commonly affects the pancreaticobiliary segment, and is characterized by diffuse or segmental narrowing of the bile ducts with long segments of narrowing and upstream dilation[21]. Inflammation in IgG4-SC typically involves the entire thickness of the bile duct wall, particularly the submucosal and subserosal layers, with relatively less damage to the epithelial layer[22]. In contrast, PSC cholangiography usually shows band-like strictures, beaded or pruned tree appearance, and diverticulum-like changes[23], and cholangiocarcinoma originates from the epithelial layer and is characterized by its invasive growth. Contrast-enhanced CT reveals that a hallmark of IgG4-SC is the uniform enhancement of the bile duct walls during the arterial phase, whereas in cholangiocarcinoma, the bile duct wall exhibits dual-layer enhancement. The smoothness of the inner lumen and outer layer are also characteristic of IgG4-SC[24,25]. Although differential diagnosis using CTs or MRIs poses certain challenges, an advantage lies in the ability to detect tumor invasion and extrabiliary metastatic lesions. US results are nonspecific and cannot differentiate IgG4-SC from PSC or cholangiocarcinoma[26]. EUS or IDUS offer higher resolution, with EUS also aiding in obtaining tissue samples[27,28]. IDUS can display the stratified structure of the bile duct wall with high resolution, showing characteristics including circular symmetric wall thickening, smooth inner and outer edges, and uniform internal echoes at the site of biliary strictures. Additionally, wall thickening in non-strictured areas is also characteristic of IgG4-SC[16,29,30], thus IDUS can relatively clearly reflect the pathological differences between IgG4-SC, PSC, and cholangiocarcinoma. After imaging examinations, two aspects should be evaluated: Characteristic cholangiographic features and bile duct wall thickness[11]. Characteristic cholangiographic features may help differentiate IgG4-SC from PSC. Cholangiography is useful for the differential diagnosis of diffuse strictures. However, in cases with localized strictures, diagnosing based on cholangiographic features alone has certain limitations. Nevertheless, for cases with localized strictures, endoscopic biopsy through the Vater's papilla is essential to rule out cholangiocarcinoma, although the sensitivity for detecting malignant tumors (55%-72%) is relatively low[11].

In patients with isolated IgG4-SC that are difficult to diagnose, a steroid trial may also be considered to assist in diagnosis. This involves assessing the resolution of findings on cholangiographic images obtained through CT/endoscopic retrograde cholangiopancreatography (ERCP)/magnetic resonance cholangiopancreatography after administering a steroid dose of 0.4-0.6 mg/kg for 1 or 2 weeks. If there is no improvement, a reevaluation is necessary to consider other possible diseases[11]. Before and after the commencement of steroid treatment, regular follow-ups are required to assess symptoms and signs, perform blood biochemical tests, measure IgG/IgG4 Levels, and conduct imaging studies. Additionally, attention must be paid to signs of relapse, the exclusion of malignant lesions, and the management of adverse reactions to steroids[11].

In recent years, research has discovered that Annexin A11 serves as an autoantigen in both IgG4-SC and AIP[31]. Additionally, Yukari Kato and colleagues reported a case of IgG4-SC diagnosed through the detection of antibodies against laminin 511-E8, despite normal serum IgG4 concentrations and no evidence of IgG4 plasma cell infiltration in the bile ducts[32]. A prospective study found that IgE levels can be utilized for diagnosing and predicting relapses in IgG4-RD[33]. Furthermore, studies have identified potential biomarkers such as serum IFN-α[34], peripheral plasmablast counts in treatment-naive IgG4-RD patients[35], the ratio of peripheral $CD19^{+}CD24^{-}CD38^{hi}$ subset/$CD19^{+}$ B cells in IgG4-RD patient[36], and PD-1^{+} Tfh cell counts[37] for diagnosing and monitoring the activity of IgG4-SC. However, further research is needed to confirm whether these indicators can become new specific biomarkers for IgG4-SC.

CONCLUSION

As most IgG4-SC cases are associated with AIP, IgG4-SC can be accurately diagnosed based on clinical diagnostic criteria. However, the differential diagnosis of isolated IgG4-SC currently remains challenging, especially in distinguishing it from cholangiocarcinoma, PSC, and pancreatic cancer. Methods such as CT, MRI, ERCP, IDUS, bile duct biopsy, and duodenal papilla biopsy aid in the diagnosis and differential diagnosis of isolated IgG4-SC. When these examination results do not show typical changes or when steroid treatment is ineffective, reevaluation may be necessary, potentially including pathological examination or surgery. The use of serum biomarkers discovered in recent research studies can also be considered to assist in diagnosis. Therefore, improving the diagnostic level of IgG4-SC depends on further research into its etiology and pathogenesis.

FOOTNOTES

Author contributions: He YH, Liang MX, Chen Y and He Y contributed to this paper; He YH and Liang MX designed the overall concept and outline of the manuscript, contributed to the writing, and editing the manuscript, and review of literature; Chen Y and He Y contributed to the discussion and design of the manuscript.

Supported by The Science and Technology Research Foundation of Guizhou Province, and Zunyi City, No. QKHJC-ZK (2022) YB642, No. ZSKH-HZ (2022) 344, and No. gzwjkj2021-071; The WBE Liver Fibrosis Foundation, No. CFHPC2025028; and The Beijing Gandan Phase Mutual Public Welfare Fund for Artificial Liver Project, No. iGandanF-1082024-Rgg018.

Conflict-of-interest statement: The authors declare that they have no conflict of interests.

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S-Editor: Liu H
L-Editor: A
P-Editor: Chen YX

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